REMARKS

In response to the Office Action dated October 20, 2005, Applicants submit the previous amendments and following remarks. Claim 10 has been cancelled. Claims 6, 9 and 13 are amended. Applicants have added new Claims 14-17. Applicants submit that no new matter was added by the amendments, and that support for the amendments can be found throughout the specification. Support for the amendment to Claims 6 and 9 can be found, for example, in Figure 6, SEQ ID NO:6. Support for the amendment to Claim 13 can be found, for example, at paragraph [0229]. Support for new Claims 14-17 can be found, for example, in the claims as originally filed and paragraphs [0336], [0362], [0407], and Example 17 starting at paragraph [0526].

Claims 6-9 and 11-17 are presented for examination. Applicants respond below to the specific rejections raised by the PTO in the Office Action mailed October 20, 2005. For the reasons set forth below, Applicants respectfully traverse.

Rejection Under 35 U.S.C. §101 - Utility

Claims 6-13 remain rejected under 35 U.S.C. §101 on the assertion that the claimed invention is not supported by either a specific asserted utility or a well established utility. The PTO maintains that Applicants' arguments "do not address why any general increase in TNF-α in human blood would be of substantial utility, especially in view of the fact that Goeddel *et al.* teaches (page 602) that increases in TNF-α can both inhibit the growth of cells and or stimulate the growth of cells." Office Action at 3. The PTO also asserts that Applicants' in vitro experiments would not necessarily extrapolate to any proposed in vivo therapy, and that "there is no specific or substantial nexus between the disclosed pharmacological activity and a real-world pharmacological use that provides an immediate benefit to the public." Office Action at 5.

Utility – Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic tool without also identifying the condition that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient,* at least with regard to defining a 'substantial' utility." (M.P.E.P. § 2107.01, emphasis added).

The mere consideration that further experimentation might be performed to more fully develop the claimed subject matter does not support a finding of lack of utility. M.P.E.P. § 2107.01 III cites *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995) in stating that "Usefulness in patent law ... necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." Further, "to violate § 101 the claimed device must be totally incapable of achieving a useful result." *Juicy Whip Inc. v. Orange Bang Inc.*, 51 U.S.P.Q.2d 1700 (Fed. Cir. 1999), *citing Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992).

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, in assessing the credibility of the asserted utility, the M.P.E.P. states that "to overcome the presumption of truth that an assertion of utility by the applicant enjoys" the PTO

must establish that it is "more likely than not that one of ordinary skill in the art would doubt (i.e., 'question') the truth of the statement of utility." M.P.E.P. § 2107.02 III A. The M.P.E.P. cautions that:

> Rejections under 35 U.S.C. 101 have been **rarely sustained** by federal courts. Generally speaking, **in these rare cases**, the 35 U.S.C. 101 rejection was sustained [] because the **applicant ... asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art**. M.P.E.P. § 2107.02 III B., citing *In re Gazave*, 379 F.2d 973, 978, 154 U.S.P.Q. 92, 96 (CCPA 1967) (underline emphasis in original, bold emphasis added).

Utility need NOT be Proved to a Statistical Certainty – a Reasonable Correlation between the Evidence and the Asserted Utility is Sufficient

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). *See, also In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977). Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal

evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

The M.P.E.P. states that "Courts have repeatedly found that the mere identification of a pharmacological activity of a compound that is relevant to an asserted pharmacological use provides an 'immediate benefit to the public' and thus satisfies the utility requirement." M.P.E.P. § 2107.01, part III (8th ed. 2004) (emphasis added). As the Court of Customs and Patent Appeals held in *Nelson v. Bowler*:

> Knowledge of the pharmacological activity of any compound is obviously beneficial to the public. It is inherently faster and easier to combat illnesses and alleviate symptoms when the medical profession is armed with an arsenal of chemicals having known pharmacological activities. Since it is crucial to provide researchers with an incentive to disclose pharmacological activities in as many compounds as possible, we conclude that adequate proof of any such activity constitutes a showing of practical utility. *Nelson v. Bowler*, 626 F.2d 853, 856, (CCPA 1980) (emphasis added).

In *Nelson v. Bowler*, Nelson had developed and claimed a class of synthetic prostaglandins. At the time of the application, naturally occurring prostaglandins had a recognized value in pharmacology. To support his asserted utility, Nelson's application included test results demonstrating the bioactivity of his synthetic prostaglandins relative to the bioactivity of the natural prostaglandins. The court concluded that Nelson had satisfied the practical utility requirement in identifying the synthetic prostaglandins as pharmacologically active compounds, rejecting arguments that attacked the evidentiary basis for Nelson's assertions that the compounds were pharmacologically active. *See* M.P.E.P. § 2107.01, part III (8th ed. 2004).

Similarly, in *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996), the Court of Appeals for the Federal Circuit upheld a PTO decision that *in vitro* testing of a novel pharmaceutical compound was sufficient to establish practical utility, stating the following rule:

> [T]esting is often required to establish practical utility. But the test results **need not absolutely prove** that the compound is pharmacologically active. All that is required is that the tests be "*reasonably* indicative of the desired [pharmacological] response." In other words, there must be **a sufficient correlation** between the tests and an asserted pharmacological activity so as to convince those skilled in the art, **to a reasonable probability**, that the novel

> compound will exhibit the asserted pharmacological behavior." *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996) (internal citations omitted, bold emphasis added, italics in original).

Like the present case, the *Fujikawa* case was in the context of utility for pharmaceutical compounds, and thus the same standard of utility applies – utility does not have to be established to an absolute certainty, rather, the evidence must convince a person of skill in the art "to a reasonable probability." In addition, the evidence need not be direct, so long as there is a "sufficient correlation" between the tests performed and the asserted utility.

The Court in *Fujikawa* relied in part on its decision in *Cross v. Iizuka*, 753 F.2d 1040, 224 U.S.P.Q. 739 (Fed. Cir. 1985). In *Cross*, the Appellant argued that basic *in vitro* tests conducted in cellular fractions did not establish a practical utility for the claimed compounds. Appellant argued that more sophisticated *in vitro* tests using intact cells, or *in vivo* tests, were necessary to establish a practical utility. The Court in *Cross* rejected this argument, instead favoring the argument of the Appellee:

> [*I*]*n vitro* results...are generally predictive of *in vivo* test results, i.e., there is a **reasonable correlation** therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are. [Appellee] has not urged, and rightly so, that there is an invariable exact correlation between *in vitro* test results and *in vivo* test results. Rather, [Appellee's] position is that successful *in vitro* testing for a particular pharmacological activity establishes a **significant probability** that *in vivo* testing for this particular pharmacological activity will be successful. *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739 (Fed. Cir. 1985) (emphasis added).

Taken together, these cases establish that the legal standard for demonstrating utility is a relatively low hurdle. An Applicant need only provide evidence such that it is **more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true**. The evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. The Applicant does not need to provide evidence such that it establishes an asserted utility as a matter of statistical certainty.

In response to the initial utility rejection, Applicants submitted the declaration of Dr. Paul Godowski, describing the methodology utilized in the experiments of Example 17 in which the claimed polypeptides were shown to stimulate the release of TNF-α levels in human blood. The

results demonstrate that the claimed polypeptides were able to increase the level of TNF-α to a level at least 50-fold greater than the amount normally present in human blood. In fact, as stated in the declaration, because TNF-α is present at an undetectable level in human blood, the levels of enhancement are relative to the minimal amount of TNF-α detectable under the assay conditions utilized.

Applicants submit that the Godowski Declaration and references cited therein, including Goeddel et al., establish therapeutic methods of enhancing TNF-α levels in a subject. Goeddel teaches that intravenous treatment with TNF-α of the Meth-A tumor implanted intradermally results in a cure rate of almost 100%. Goeddel at 601, right column. The PTO provides no basis to doubt that this is a reliable model for tumor treatment. In addition, that a compound can be used to successfully treat one type, but not all types, of tumor is not evidence supporting a lack of utility or enablement. "If the applicant has asserted that the claimed invention is useful for any particular practical purpose...and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility; M.P.E.P 2107 (emphasis added); "If any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention." M.P.E.P. 2164.01(c).

Goeddel teaches a successful therapeutic use of increased TNF-α levels in a subject. Applicants assert that the claimed polypeptides stimulate the release of TNF-α in blood. No more is required. The PTO presents no evidence or reasoning to doubt the asserted utility, and Goeddel supports Applicants' assertions.

Therapeutic Methods of Using TNF-α were Known in the Art

Applicants maintain that the teachings of the specification, the Godowski Declaration and the references cited therein fully support the position that one skilled in the art could make and use the claimed polypeptides without undue experimentation. Nonetheless, Applicants submit herewith four abstracts of articles reporting therapeutic methods on humans which demonstrate that perfusion with TNF-α in the blood can be used to successfully treat cancer. (Submitted herewith as Exhibits 1-4). These references were published before or within a year of the earliest priority date of the instant application and can therefore be used to demonstrate the level of skill in the art. *See AK Steel Corp. v. Sollac*, 344 F.3d 1234, 1244 (Fed. Cir. 2003) ("[T]he artisan's

knowledge of the prior art and routine experimentation can often fill gaps, interpolate between embodiments, and perhaps even extrapolate beyond the disclosed embodiments, depending upon the predictability of the art."). Thus, these references further establish that one skilled in the art would have known that compounds that enhance TNF-α levels in blood could be used to achieve useful therapeutic results.

Applicants have submitted substantial evidence demonstrating that one skilled in the art would know that compounds and methods that enhance TNF-α levels in blood could be used to achieve useful therapeutic results. Combining the knowledge in the art with the disclosure in the instant application that the claimed polypeptides stimulate the release of TNF-α in the blood, one of skill in the art would know how to use the claimed polypeptides. *See In re Bundy* 209 U.S.P.Q. 48, 51 (CCPA 1981) ("We do not consider that one of ordinary skill in the art would not know how to use these novel analogs to determine the specific dosages for the various biological purposes ... the basic pharmacological activity having been established in this case, not merely *presumed* from similar molecular structure.") (emphasis in original). Thus, Applicants have established the utility of the claimed invention.

Applicants remind the PTO that the M.P.E.P. cautions that rejections for lack of utility are rarely sustained by federal courts, and that generally speaking, a utility rejection was sustained because the applicant asserted a utility "that could **only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art.**" M.P.E.P. § 2107.02 III B., citing *In re Gazave*, 379 F.2d 973, 978, 154 U.S.P.Q. 92, 96 (CCPA 1967) (underline emphasis in original, bold emphasis added). Rather than being wholly inconsistent with contemporary knowledge in the art, Applicants' asserted utility is squarely within the teachings in the field, and is supported by references and the declaration of a skilled expert.

Finally, Applicants point out that in related pending applications claiming other PRO polypeptides that were also shown to stimulate TNF-α release in human blood, the utility of the polypeptides has been accepted by the USPTO. See for example Applications No. 10/063,588 and No. 10/063,664.

Specific Utility

Applicants next address the PTO's assertions the claimed polypeptides lack a specific asserted utility. Applicants respectfully disagree.

Specific utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. § 2107.01 I. Applicants submit that the evidence set forth in the specification of stimulation of TNF-α release in blood by PRO263, along with the declaration and references discussed above, provide a specific utility for the claimed polypeptides.

As discussed above, there are significant, reliable and reproducible data which show that the PRO263 polypeptide stimulated the release of at least 50-fold more TNF-α than compared to the control. The Declaration of Dr. Godowski discusses several references which associate TNF-α with the treatment of diseases, as do Exhibits 1-4 submitted herewith. Use of the PRO263 polypeptides and antibodies to regulate the stimulation of TNF-α release is a specific utility – it is not a general utility that would apply to the broad class of polypeptides and antibodies.

Conclusion

Applicants provided the Declaration of Paul Godowski stating that the data in Example 17 are real and significant. This declaration also indicates that given the at least fifty-fold increase in TNF-α levels, the disclosed polypeptides and antibodies have utility as therapeutic tools. The Declaration, accompanying references, and references submitted herewith demonstrate that it is well-established in the art that there are several conditions in which regulation of TNF-α release is beneficial. The PTO has not offered any substantial reasoning or evidence to the contrary.

The PTO also asserts that there is no asserted specific utility. Applicants have pointed out that the substantial utilities described above are specific to the disclosed polypeptides because the PRO263 polypeptide stimulates TNF-α release in blood. This is not a general utility that would apply to the broad class of polypeptides.

Given the totality of the evidence provided, Applicants submit that they have established a substantial, specific, and credible utility for the claimed polypeptides and related antibodies as therapeutic tools. According to the PTO "the mere identification of a pharmacological activity of

a compound that is relevant to an asserted pharmacological use provides an 'immediate benefit to the public' and thus satisfies the utility requirement." M.P.E.P. § 2107.01, part III (8th ed. 2004) (emphasis added). In addition, the Courts have held that "the test results need not absolutely prove that the compound is pharmacologically active. All that is required is that the tests be '*reasonably* indicative of the desired [pharmacological] response.'" *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996) (internal citations omitted, italics in original).

Finally, according to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is not required. Rather, a specific, substantial, and credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants remind the PTO that:

> A small degree of utility is sufficient . . . The claimed invention must only be capable of performing **some** beneficial function . . . An invention does not lack utility merely because the particular embodiment disclosed in the patent lacks perfection or performs crudely... A commercially successful product is not required... Nor is it essential that the invention accomplish all its intended functions... or operate under all conditions... partial success being sufficient to demonstrate patentable utility... In short, **the defense of non-utility cannot be sustained without proof of total incapacity**. If an invention is only partially successful in achieving a useful result, a rejection of the claimed invention as a whole based on a lack of utility is not appropriate. M.P.E.P. at 2107.01 (underline emphasis in original, bold emphasis added, citations omitted).

In view of the above, Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the claimed PRO263 polypeptides set forth in the specification. Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejections under 35 U.S.C. § 112, first paragraph – Enablement

The PTO also rejects Claims 6-13 under 35 U.S.C. § 112, first paragraph, stating that because the claimed invention is not supported by either a specific asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention.

Applicants submit that in the discussion of the 35 U.S.C. § 101 rejection above, Applicants have established a substantial, specific, and credible utility for the claimed

polypeptides. Applicants respectfully request that the PTO reconsider and withdraw the enablement rejection under 35 U.S.C. §112.

Rejection under 35 U.S.C. §112, first paragraph – Written Description

The PTO rejects Claims 6, 9, 12-13 and amended Claim 10 under 35 U.S.C. § 112, first paragraph, as failing to satisfy the written description requirement. The PTO asserts that SEQ ID NO:5 fails to provide any support for the claimed sequences, and disclosure of a complete amino acid sequence does not provide a written description or evidence of contemplation for any specific regions within that sequence. Thus, there is no clear support in the specification and the claims as originally filed for the recitation of amino acids 17-234 of the polypeptide of SEQ ID NO: 6.

Applicants note that the reference to SEQ ID NO:5 in their previous arguments was a typographical error. Applicants intended to refer to SEQ ID NO:6. Figure 6, SEQ ID NO:6, discloses the presence of a signal sequence at amino acids 1-16 and a transmembrane domain at amino acids 235-254. The claimed invention is therefore fully disclosed in the specification as filed.

In addition, newly added Claims 14-17 are related to isolated polypeptides having at least 95% or 99% amino acid sequence identity to several polypeptides related to SEQ ID NO:6, and meet the limitation "wherein said isolated polypeptide or a fragment thereof can be used to generate an antibody which can be used to specifically bind the polypeptide of SEQ ID NO:6."

Applicants maintain that there is no substantial variation within the species which fall within the scope of these claims, which require at least 95% or 99% amino acid sequence identity to the disclosed sequences related to SEQ ID NO:6, and the ability to generate an antibody specific to PRO263. Applicants note that these claims are analogous to the claims discussed in Example 14 of the written description training materials. In Example 14, the written description requirement was found to be satisfied for claims relating to polypeptides having 95% homology to a particular sequence and possessing a particular catalytic activity, even though the applicant had not made any variants. Similarly, Claims 14-17 also have very high sequence homology to the disclosed sequences and must share the function of being useful to generate an antibody which can be used to specifically bind the polypeptide of SEQ ID NO:6.

Accordingly, Applicants respectfully request that the PTO reconsider and withdraw the written description rejection under 35 U.S.C. §112.

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

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